Facile and Efficient Chemical Functionalization of Aliphatic Polyesters by Cross Metathesis

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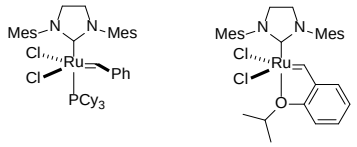
An effective preparation of new tailor-made macromolecular materials via the combination of two (atom-efficient) catalytic transformations is reported. First, new aliphatic polyesters with alternated composition have been prepared using a salen aluminum catalyst system. Next, the pendant vinyl moieties in those copolymers have been selectively transformed into various functional groups by metathesis in the presence of homogeneous Grubbs catalysts. The latter metathesis reaction has been optimized in terms of catalytic activity and selectivity, to define the conditions for an effective and safe procedure that does not affect the macromolecular architecture. All polymer materials have been microstructurally analyzed by ^{1}H, and ^{13}C NMR spectroscopy, to diagnose the catalyst selectivities in the copolymerization and metathesis processes.

Introduction

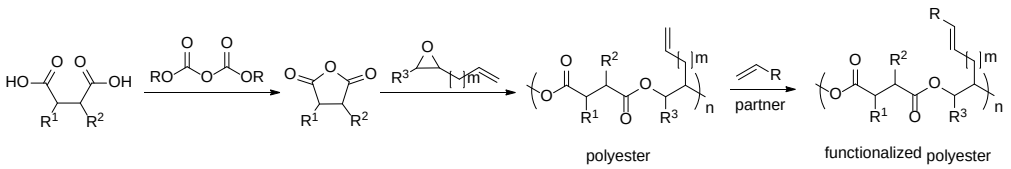
Among the most promising biodegradable polymers, aliphatic polyesters are of particular interest, since they have given rise to a broad range of practical applications from packaging to more sophisticated biomedical devices. Current methods to synthesize aliphatic polyesters include ring-opening polymerization (ROP) of cyclic esters, alternating ring-opening copolymerization of epoxides and anhydrides and polycondensation of diols and diacids.[1] Over the past two decades, ring-opening polymerization catalysts have been used to produce aliphatic polyesters with excellent structural control.[2] Advances in (stereo)control afford polymers with precise organization,[3] and the development of living catalysts has provided the opportunity to synthesize polyesters of defined molecular weight and sequence.[4] In order to further extend the applications of these polymers, it is necessary to vary and finely tune their physico-chemical properties. The living character of the polymerization reactions offers the opportunity to prepare new exciting copolymers, thereby increasing the potential of the resulting materials in terms of modulated thermal, physical or mechanical properties.[1] In this regard, regularly alternating polymers allow optimal positioning of functional substituents and should be useful in a variety of applications. It has been shown that alternating polyesters with diverse degradation rates dependent on the monomer composition can be produced by incorporating different monomers.[5,6] However, polyesters are currently far from being optimal and tailor-made structures are still needed. In particular, the introduction of functional groups is highly desirable in an effort to impart hydrophilicity and to allow post-polymerization derivatization. However, an inherent liability of most ring-opening (co)polymerization catalysts is their inability to incorporate functionality that is often desired to modify physical properties, or chemical reactivity of a polymer.[7-14]

In recent years, olefin metathesis has emerged as a powerful synthetic technique in polymer chemistry.[15] Notably, the development of active and robust ruthenium catalysts such as **1**-**2** (Figure 1), which combine high activity with an impressive functional-group tolerance, has allowed cross metathesis (CM) between small molecules to provide direct access to a large number of functionalities from terminal olefins.[16]



(**1**) (**2**)

Figure 1 Catalysts used in this study



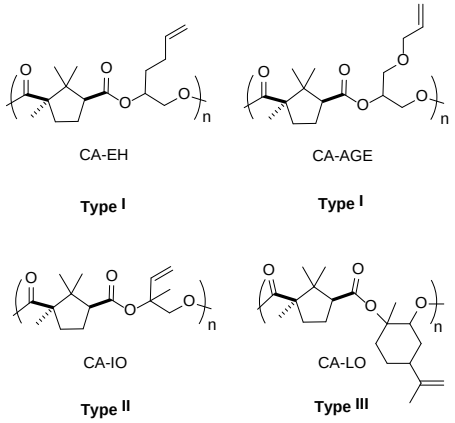
Scheme 1 Synthesis of functionalized polyesters

Therefore, CM should represent a convenient route to functionalized materials by post-polymerization modification.[17] However, there are very few reports of CM reactions between polymers and small molecules, and those have been performed on robust polyolefins[18] and poly(2-oxazoline).[19] Furthermore, CM has not been applied to the post-functionalization of (biodegradable) polyesters. Herein we report the chemical modifications of new biomaterials by post-polymerization modification of alkene-containing polyester architectures using cross-metathesis functionalization.

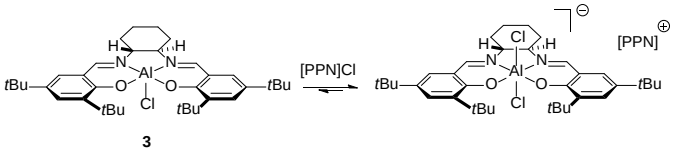
Results and discussion

The first objective of our post-polymerization functionalization study was the synthesis of various (new) polyesters with terminal pendant olefin group. Recently, several research groups described the activity of efficient catalysts in the synthesis of alternating polyesters from cyclic anhydrides and epoxides by ROP, affording a large variety of structures under mild reaction conditions.[20] Although these ROP catalysts are quite effective, the copolymerization of cyclic anhydrides[21] with epoxides bearing pendant vinyl groups is essentially unprecedented in the literature.[22-24] Such a copolymerization should lead to polyesters with olefin groups, offering unique opportunities for further chemical functionalization. In a preliminary study, we have reported an efficient preparation of new tailor-made aliphatic polyesters by combining two consecutive catalytic transformations.[24] This combination consists in the cyclization of bio-sourced dicarboxylic acids, followed by subsequent copolymerization of the corresponding cyclic anhydrides with epoxides. With this convenient method in hand, we envisaged that epoxides with double bond moiety could be used to introduce pendant olefin functions in the alternating polyester chains (Scheme 1).

In order to develop a straightforward methodology to prepare functionalized alternating copolymers, we chose to target our efforts on camphoric-based polyesters, easily accessible from the corresponding dicarboxylic acid. Indeed, we previously observed that camphoric-based copolymers were obtained with narrow polydispersities on a large synthetic scale.[24] We hypothesized that these polyesters should allow an easy identification of undesired cross-linking during the olefin metathesis reactions by size-exclusion chromatography analysis. In this regard, Grubbs et al. proposed a general empirical model for olefin reactivity which can be used to predict both selective and nonselective cross metathesis reactions for a number of commercially available metathesis catalysts.[25] The authors reported general ranking of olefin reactivity in CM by categorizing olefins by their relative ability to undergo homodimerization via cross metathesis and the susceptibility of their homodimers toward secondary metathesis reactions. According to this categorization, we considered the copolymerization of bio-sourced and sterically congested epoxides (*i.e.*, isoprene monoxide (IO) and limonene oxide (LO)), and less hindered epoxides, such as allyl glycidyl ether (AGE) and 1,2-epoxy-5-hexene (EH), to investigate a panel of olefin types. We hypothesized that CA-LO would react as a type III olefin since the alkene function is gem-disubstituted and one of the substituents is a hindered aliphatic cycle, CA-IO as a type II olefin due to the sterically congested substituent, and CA-AGE and CA-EH as type I olefins since the alkene functions are terminal and away from electron-withdrawing groups (Scheme 2). Firstly, we investigated the tandem synthesis of these camphoric-based copolymers. Table 1 summarizes typical results obtained under different polymerization conditions.



Scheme 2 Structures of various polyesters synthesized by tandem catalysis



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Scheme 3 Formation of the aluminum active species in the presence of the salen complex **3** and [PPN]Cl.

The copolymerization of camphoric anhydride (CA) and suitable epoxides was investigated with a catalyst system based on the salen aluminum chloride complex (**3**) and [PPN]Cl ([PPN] = bis(triphenylphosphoranylidene)iminium) as a co-catalyst (Scheme 3). After a cyclization step (Scheme 1), copolymerizations were carried out either in bulk (Table 1,

entries 1-3) or in a toluene solution (Table 1, entry 4). Neat conditions were optimal for reactions performed without toluene. The resultant polymers reveal narrow molecular-weight distributions and experimental number-average molecular masses (M_n) close to the theoretical ones. Poly(epoxy hexene camphorate) (CA-EH) was synthesized at 60°C in neat EH (500 eq.) with 100 eq. of camphoric acid (Table 1, entry 1). Due to increased viscosity, a larger amount of AGE (850 eq.) was used affording total conversion of camphoric anhydride after only 3h (Table 1, entry 2). The copolymerization of camphoric anhydride with isoprene monoxide required longer reaction time (26h) to provide moderate yield (Table 1, entry 3). We hypothesized that this lower reactivity could be explained by steric hindrance. Finally, CA-LO was formed in toluene by using higher temperature and larger amount of co-catalyst to obtain the resulting copolymer (Table 1, entry 4). The final reaction mixtures and copolymers were analyzed by ^{1}H, ^{13}C NMR, GPC and DSC, allowing the determination of monomers conversion and detailed characterization of the copolymers. Thereafter, functionalization of the pendant vinyl groups in these polymers was studied. We explored CM reactions of a range of commercially available partners with alternating polyesters (Table 2) catalyzed by Grubbs' ruthenium carbene complex (**1**) or Hoveyda-Grubbs second-generation catalyst (**2**). These systems are remarkably tolerant of functional groups and are efficient for a variety of cross-metathesis reactions.

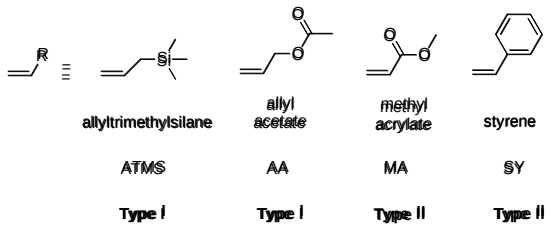

Fig. 2 CM partners for the functionalization of polyesters.

We decided to focus our first efforts on cross-metathesis functionalization involving methyl acrylate (MA) and allyltrimethylsilane (ATMS) (Figure 2). The yields for the CM reactions of alkene containing polymers were determined by the integration of ^{1}H NMR alkene resonances of the starting polyester (δ = 5.8 ppm) and the product copolymer. GPC chromatographs of functionalized polyesters showed slight changes in M_n but constant molecular weight distributions versus their unfunctionalized precursors, reflecting a change in hydrodynamic volume but no chain-degradation or cross-linking of the functionalized polymers (Table 2, entries 1-4). We first investigated the reactivity of Grubbs second-generation catalyst **1** with CA-AGE. The empirical model states that different types of CM partners reacting with each other would give selective cross metathesis. Since CA-AGE can be considered as a type I olefin, we focused on the use of a type II partner as methyl acrylate to obtain optimum selectivity.[26] Generally, second-generation catalyst **1** performs well in the CM of acrylates and terminal double bonds (Figure 2).[27,28] Indeed in the presence of 5 mol% of **1**, we observed a satisfying conversion in CA-AGE-MA after 22h reaction (Table 2, entry 1). In order to improve the reactivity, the same reaction was conducted in the presence of **2** and a higher yield of the functionalized copolymer was obtained (Table 2, entry 2). When the catalyst loading was increased to 15 mol%, higher conversion of CA-AGE was achieved in 22h (Table 2, entry 3). Interestingly, it is worth noting that no trace of self-macromolecular metathesis reaction was observed by ^{1}H NMR spectroscopy (*i.e.*, no multiplet at 5.3 ppm) (Figure 3).[‡] Also, using the same procedure, CA-EH was completely converted into CA-EH-MA (Table 2, entry 4).

Table 1 Tandem synthesis of camphoric-based polyesters.[a]

Entry	Epoxide	[PPNCl]/[M]	[A]/[E]	T. (ºC)	Solvent	Time (h)	Conversion[b] (%)	M_n[c] (g.mol^{-1})	PDI[c]
1	EH	2	5	60	-	19	79	14360	1.3
2	AGE	2	8.5	60	-	3	99	10020	1.4
3	IO	2	5	60	-	26	69	6690	1.2
4	LO	5	1	100	toluene	24	74	10300	1.3

[a] Copolymerization performed after cyclization step with [anhydride]/[M] = 100. [b]As determined by the integration of ^{1}H NMR. [c] M_n and M_w/M_n of polymer determined by SEC-RI in THF at RT using polystyrene standards.

Table 2 Cross metathesis of functionalized polyesters.[a]

Entry	Catalyst	Polymer	M_n[b] (g.mol^{-1})	M_w/M_n[b]	Partner	[P]/[M] (mol%)	Time (h)	Conv.[c] (%)	M_n[b] (g.mol^{-1})	M_w/M_n[b]
1	**1**	CA-AGE	9840	1.7	MA	5	22	74	10880	1.6
2	**2**	CA-AGE	9250	1.7	MA	5	22	91	9430	1.2
3	**2**	CA-AGE	9500	1.4	MA	15	22	93	9400	1.5
4	**2**	CA-EH	14360	1.3	MA	10	70	99	15740	1.2
5	**2**	CA-LO	8700	1.3	MA	15	70	traces	ND[d]	ND
6	**2**	CA-LO	8700	1.3	ATMS	15	70	traces	ND	ND
7	**2**	CA-IO	7400	1.3	MA	15	70	traces	ND	ND
8	**2**	CA-IO	7400	1.3	ATMS	15	70	traces	ND	ND

[a] All reactions performed at reflux of methylene chloride. [b] M_n and M_w/M_n of polymer determined by SEC-RI in THF at RT using polystyrene standards. [c] Determined by ^{1}H NMR integration. [d] Not determined.

For more hindered type III olefins, such as CA-IO and CA-LO, no cross-metathesis product was obtained with a type I partner (ATMS), even though the catalytic loading was higher (Table 2, entries 5-8). Therefore, cross metathesis is very sensitive to the steric hindrance of the epoxide bearing the alkene, but also probably to the nature of the anhydride.

With an efficient synthesis of functionalized copolymers in hand, we then studied cross metathesis of CA-AGE with various type I and type II partners in the presence of 15 mol% of Hoveyda-Grubbs II catalyst **2** (Table 3).

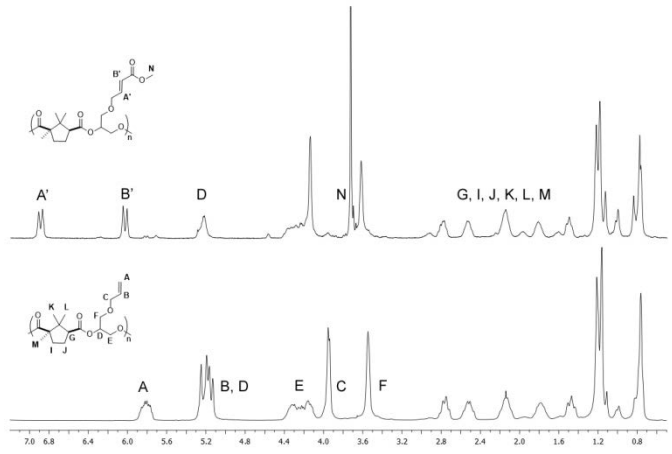

Fig. 3 ^{1}H NMR Spectra of the poly(allyl glycidyl camphorate) functionalized by MA (entry 5, top) and poly(allyl glycidyl camphorate) (bottom) (300MHz, $CDCl_3$).

Styrene (SY) provided a suitable model for introducing aromatic branching in the polymers, while methyl acrylate and allyl acetate (AA) were chosen as a way to add non-protic polarity. Also allyltrimethylsilane (ATMS) was identified as an interesting hydrophobic coupling partner.[29]

Under these reaction conditions, the yield always exceeds 90%, and the experimental M_n values correspond well with the calculated M_n values (Table 3, entries 1-4). Finally, the polymers produced still exhibited relatively narrow molecular weight distributions (M_w/M_n = 1.4-1.8).

Table 3 Influence of metathesis partners on CA-AGE copolymer.[a]

Entry	M_n[b] (g.mol^{-1})	M_w/M_n[b]	Partner	Time (h)	Conv.[c] (%)	M_n[b] (g.mol^{-1})	M_w/M_n[b]
1	9500	1.4	MA	22	93	9400	1.5
2	10500	1.6	SY	70	91	8340	1.8
3	10500	1.6	AA	70	91	10800	1.5
4	10500	1.6	ATMS	70	99	15400	1.4

[a] All reactions performed at 40°C in methylene chloride with 15 mol% of Hoveyda-Grubbs II catalyst and 6 equivalents of partner. [b] M_n and M_w/M_n of polymer determined by SEC-RI in THF at RT using polystyrene standards. [c] Determined by ^{1}H NMR integration.

Table 4 DSC analysis on functionalized polyesters.[a]

Entry	Copolymer	M_n[a] (g.mol^{-1})	M_w/M_n[a]	T_g (°C)
1	CA-AGE	9500	1.4	6
2	CA-EH	14360	1.3	23
3	CA-IO	7400	1.4	42
4	CA-LO	7100	1.3	112
5	CA-AGE-MA	10700	1.6	47
6	CA-AGE-SY	9200	1.7	96
7	CA-AGE-AA	7700	1.6	81
8	CA-AGE-ATMS	15400	1.4	50
9	CA-EH-MA	15740	1.2	29

[a] M_n and M_w/M_n of polymer determined by SEC-RI in THF at RT using polystyrene standards.

In order to evaluate the impact of the functionalization induced by metathesis, we analyzed thermal properties of the functionalized polyesters by differential scanning calorimetry (DSC). As a control experiment, CA-AGE, CA-EH, CA-IO and CA-LO exhibited glass transition temperatures at 6°C, 23°C, 42°C and 112°C respectively (Table 4, entries 1-4). For functionalized CA-AGE copolymers, DSC analyses showed that introduction of different partners had an important influence on the glass transition temperatures of these polymers. We observed differences in the copolymer glass transition temperatures depending on the nature of the partners used. The T_g values of these polyesters were found in the range of 47 to 96°C, which is a momentous increase as compared to the glass transition temperature (6°C) of the parent copolymer (entries 5-8). By contrast, DSC analyses showed that introduction of MA in CA-EH had only a limited influence (Table 4, Entry 9). However, it is interesting to note that these T_g values compare well those determined for syndiotactic-enriched poly(hydroxybutyrate)s (T_g = 21 to 25°C) prepared by ring-opening polymerization of *rac*-BBL with bis(phenolate) yttrium initiators.[30-32]

Conclusions

In conclusion we have demonstrated the possibility to prepare new tailor-made polymers using alternating ring-opening copolymerization followed by functionalization via cross metathesis of the corresponding alkene-containing polyesters. DSC analyses showed that introduction of different metathesis partners had a significant influence on the glass transition temperatures of these copolymers. This approach offers a real advantage to easily discover new interesting polymers. Our future work will explore the development of new alkene-containing polymers suitable for CM functionalization, as well as the modification of the pendent olefins with other functional groups.

Acknowledgements

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Notes and references

‡ A self-metathesis experiment was performed using CA-AGE without an olefinic partner and no self-metathesis of the corresponding copolymer was observed.

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